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REVIEW

Telbivudine in the Treatment of Chronic Hepatitis B

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ABSTRACT

Introduction: The treatment of chronic hepatitis B virus (HBV) infection has been revolutionized in the past decade by the increased availability of effective antiviral agents. Telbivudine is an L-nucleoside that is structurally related to lamivudine and has recently been approved for use in patients with chronic HBV infection. Telbivudine is highly selective for HBV DNA and inhibits viral DNA synthesis with no effect on human DNA or other viruses. This article reviews the pharmacology, pharmacokinetics, therapeutic efficacy and safety of telbivudine, and discusses its place in the current armamentarium against HBV. ***Methods:*** Relevant publications were identified from searches of Medline and PubMed between 2000 and 2008, using the search terms "hepatitis B/HBV," "telbivudine/LdT," "β-L-thymidine," "pharmacokinetics," "safety," "adverse events," and "resistance." The reference lists of retrieved articles were searched for relevant studies. ***Results:*** Phase 3 clinical studies demonstrate that telbivudine is superior to lamivudine over a 2-year period in hepatitis B e-antigen (HBeAg)-positive and HBeAg-negative patients. Telbivudine was associated with a statistically signficantly greater reduction in HBV DNA, greater proportion of alanine aminotransferase normalization, and greater histological response than lamivudine. Furthermore, telbivudine use resulted in fewer cases of treatment failure and less virological resistance than lamivudine. However, after 2 years of therapy, telbivudine resistance was appreciable (25%) and considerably higher than that seen with other new antivirals such as tenofovir and entecavir. Overall, telbivudine was found to be safe, although grade 3 or 4 adverse events, including elevations in creatine kinase, were more commonly found in patients receiving telbivudine than lamivudine. Telbivudine is not active against lamivudine-resistant HBV. ***Conclusions:*** Telbivudine is a new antiviral agent joining the armamentarium against

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HBV. It is superior to lamivudine in terms of therapeutic response and resistance profile. However, concerns about resistance with long-term use, along with inferior cost-effective analyses, have relegated telbivudine to a second-line agent in the management of chronic HBV infection.

Keywords: hepatitis B; resistance; telbivudine; treatment

INTRODUCTION

Despite the introduction of an effective vaccine more than 25 years ago, hepatitis B virus (HBV) infection remains a significant global health problem worldwide.[1] An estimated 2 billion people have been infected, with 400 million individuals remaining chronic carriers, resulting in over a million deaths every year.[2] The majority of HBV carriers never develop significant liver disease, but some 15%-40% develop life-threatening complications eventually, including cirrhosis, liver failure, and hepatocellular carcinoma (HCC).[3] A very small minority can be cured with interferon alfa[4-6] but otherwise, prospects for a cure are poor. The general strategy is careful identification of those with liver disease who can be offered antiviral therapy with the aim of long-term control of HBV replication, and continued surveillance of those without liver disease who remain at risk of developing cirrhosis and HCC.

Due to the significant morbidity and mortality associated with chronic infection, antiviral agents targeting HBV have emerged as a major area of research. Telbivudine (Sebivo®, Tyzeka®; Novartis, Basel, Switzerland) was approved by the US Food and Drug Administration in October 2006 for the treatment of active chronic HBV infection in adults (age ≥16 years). The drug was approved in the European Union in February 2007, launched in Germany and the UK in August 2007, and in China in December 2007. This review summarizes the pharmacology and pharmacokinetics, therapeutic efficacy, and safety of telbivudine in the management of adult patients with chronic HBV. In addition, the place of this agent in the expanding arena of nucleoside/nucleotide antiviral agents targeting HBV is discussed.

Natural History of HBV

The natural history of chronic HBV infection is characterized by different phases.[7,8] In the immune-tolerant phase there are high levels of viremia (HBV DNA levels usually $>10^6$ IU/mL) and e-antigen (eAg) positivity. Alanine aminotransferase (ALT) levels are usually normal and, if undertaken, liver biopsy often shows little inflammation or scarring. During immune reactivation, eAg seroconversion may occur with loss of hepatitis B e-antigen (HBeAg) and development of antibody to HBeAg (anti-HBe). The amount of inflammation, necrosis, and fibrosis at this point influences the prognosis of chronic HBV infection. Some patients pass through this phase easily and sustain little in the way of liver disease. In others, active viral replication can persist (often without symptoms) and the patients can sustain marked liver disease. Once eAg seroconversion has occurred many patients will retain control of the virus and have low viral DNA levels without any further liver inflammation. A significant number, however, develop mutants in the precore and basal core promoter regions of HBV, leading to active viral

replication in the presence of anti-HBe positivity.[9,10] Chronic HBeAg-negative HBV can follow an aggressive course, may lead to the rapid development of cirrhosis and HCC, and requires long-term or even indefinite treatment.

Treatment of Chronic HBV

The ultimate aim of treatment for chronic HBV infection is eradication of HBV before it causes irreversible liver damage or cancer. The complex lifestyle of the virus, however, makes this goal impossible for most patients. HBV DNA is capable of integrating into host DNA, allowing continued production of viral transcripts.[11] Furthermore, viral DNA exists in the hepatocyte nucleus as covalently closed circular DNA (cccDNA) that serves as a template for HBV replication without the need for reinfection.[12,13] As current antiviral agents have little inhibitory effect on cccDNA, there is a high relapse rate after discontinuation of treatment and prospects for eradication of HBV are poor. Therefore, therapy aims to achieve durable viral suppression leading to reduced morbidity and mortality by decreasing rates of cirrhosis, liver failure, and HCC. In HBeAg-positive patients, an additional aim of treatment is the loss of HBeAg with seroconversion to anti-HBe. Loss of hepatitis B surface antigen (HBsAg) is highly desirable but seldom achieved.

Until recently, the only drug available for treatment of HBV infection was interferon alfa.[4] New nucleoside/nucleotide analogs have emerged in the past decade with potent activity against HBV through inhibition of the viral polymerase by chain termination. Lamivudine, adefovir and, more recently, entecavir and tenofovir, are established antiviral agents in clinical use for chronic HBV infection. Other agents including emtricitabine, clevudine, and telbivudine are in use or likely to be available soon.[14]

Interferon alfa, and the newer pegylated interferon alfa-2a, are generally considered first-line therapy for chronic HBV provided there are no contraindications to their use (eg, decompensated cirrhosis or significant comorbid medical conditions).[4-6] Interferon therapy is of finite duration aiming to achieve sustained responses after treatment cessation. It induces HBeAg seroconversion in around 20%-35% of patients with pretreatment ALT levels exceeding twice the upper limit of normal.[5] In addition, interferon therapy gives an improved albeit low chance of achieving HBsAg seroconversion and no emergence of viral resistance. However, most patients fail to respond and some are ineligible for interferon therapy because of advanced disease or concurrent medical conditions. Furthermore, treatment is expensive and poorly tolerated due to frequent side effects and the requirement for self-injection.

Antiviral therapy with oral nucleosides/nucleotides provides a treatment course of indefinite duration, aiming to suppress HBV replication without emergence of viral resistance. This type of therapy is generally well tolerated and easily administered orally. Seroconversion rates and histology improve with extended therapy; however, responses are poorly maintained after treatment cessation and viral resistance emerges relatively easily. For example, with lamivudine monotherapy HBV resistance develops in 24% of patients after 1 year of therapy and in 70% after 4 years.[15] Resistance to adefovir occurs less often than lamivudine but increases with length of treatment such that 29% of nucleoside-naïve patients treated with this agent have resistance after 5 years of therapy.[16]

Entecavir and tenofovir have potent antiviral activity and a high genetic barrier against resistance and are now firmly established in the treatment armamentarium.[17,18]

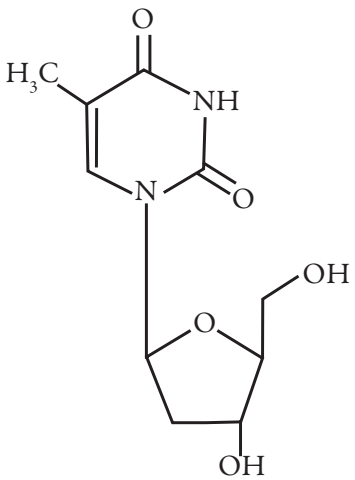
METHODS

The search terms "hepatitis B/HBV," "telbivudine/LdT," "β-L-thymidine," "pharmacokinetics," "safety," "adverse events," and "resistance" were used to conduct an English language search of PubMed and Medline between 2000 and 2008. Additional publications were identified from the reference lists of retrieved articles and meeting abstracts from the Annual Meeting of the American Association for the Study of Liver Diseases, and European Association for the Study of the Liver.

TELBIVUDINE

Telbivudine is a new orally bioavailable antiviral drug with potent activity against HBV in vitro and in animal models. It is a synthetic thymidine β-L-nucleoside analog with the chemical name 1-(2-deoxy-β-L-ribofuranosyl)-5-methyluracil (Figure 1). Telbivudine is efficiently phosphorylated by human cellular kinases to its active 5´-triphosphate form that competes with the natural substrate thymidine triphosphate, and inhibits both viral reverse transcriptase and DNA polymerase.[19,20] Incorporation of the 5´-triphosphorylated form into viral DNA inhibits DNA-dependent DNA synthesis, resulting in inhibition of HBV replication. Telbivudine inhibits both first-strand HBV DNA replication and second-strand replication, with an apparent preferential inhibition of second (+) strand synthesis.[21] In an in-vitro model, telbivudine triphosphate bound preferentially to the HBV DNA polymerase and there was no effect on human DNA polymerase, mitochondrial function, or morphology.[22] Furthermore, telbivudine is highly selective for HBV, lacking activity against other viruses including HIV-1.

Figure 1. Chemical structure of telbivudine.



Pharmacokinetics

Preclinical pharmacological studies in woodchucks and monkeys demonstrated that telbivudine was well absorbed with an oral bioavailability of 68%.[23] Telbivudine underwent minimal hepatic metabolism and the major pathway of elimination appeared to be by renal clearance of the unchanged drug.

In human studies, telbivudine was rapidly absorbed orally with the time to reach maximum plasma concentrations ranging from 1 to 4 hours after administration.[24,25] Absorption was unaffected by food.[26] In a double-blind, placebo-controlled, dose-escalation study pharmacokinetic parameters of drug exposure (maximum concentration of the drug in the plasma and the area under the plasma concentration curve)

were dose-proportional between 25 and 800 mg per day.[27,28] No metabolites were noted during metabolic investigation and telbivudine does not appear to be a substrate for cytochrome P450 isozymes.[25]

Early studies reported that the elimination of telbivudine from plasma was monophasic over an 8-hour sampling period with a mean half-life of 2.5-5.0 hours.[28] Extended sampling, however, revealed a terminal phase beginning more than 12 hours after dosing and giving a long terminal half-life of approximately 40-50 hours.[24] This indicates a sustained exposure of the drug and supports once-daily dosing.

The pharmacokinetics of other antivirals (eg, lamivudine, adefovir, entecavir) are altered in patients with renal impairment due to diminished renal clearance. No adjustment of telbivudine dose is necessary with mild renal impairment (creatinine clearance 50-80 mL/min) whereas dose adjustment is warranted for those with moderate (creatinine clearance 30-49 mL/min) to severe (creatinine clearance <30 mL/min) renal impairment or end-stage renal disease in order to achieve optimal plasma exposure.[29] Dose reduction is achieved by extending the dosing interval to every 2, 3, or 4 days. Reduction in daily dose is generally preferred over dose interval adjustment because of anticipated better compliance; however, this will require an oral solution that is not yet commercially available for telbivudine.

In an open-label, parallel-group study, no significant difference was noted in the pharmacokinetics of a single 600 mg dose of telbivudine between those with normal liver function and those with hepatic impairment.[25] Thus, dose adjustment of telbivudine is not necessary in patients with liver impairment and normal kidney function.

Clinical Efficacy

Preclinical Studies

In-vitro and animal studies provided the first indication of the high potency and selectivity of telbivudine against HBV.[22] The in-vitro median effective concentration of telbivudine for reducing extracellular DNA levels in a HBV-expressing hepatoma cell line was 0.19 μM. In the woodchuck model of HBV infection, viral replication was inhibited within the first few days of treatment and was maintained throughout the treatment period, with decreases in HBV viremia by as much as 8 logs. Following drug withdrawal, viral rebound occurred with viral levels approaching pretreatment levels between week 4 and week 8.[22]

Phase 2 Trials

In a placebo-controlled, double-blind study, adult Asian patients with chronic compensated HBeAg-positive HBV were randomized to receive escalating doses of telbivudine between 25 and 800 mg/day for 4 weeks.[27,28] Telbivudine induced striking dose-related suppression of serum HBV DNA levels with mean reductions of 3.5-4 $\log_{10}$ copies/mL after 4 weeks at dosages of 400-800 mg/day. Most patients achieved at least a 2 $\log_{10}$ reduction in HBV DNA levels in the first week of treatment. While a more profound virological response was achieved with higher plasma drug exposure, a nearly maximal viral load reduction was obtained with telbivudine doses in the 400-800 mg range.

Lai et al. compared telbivudine to lamivudine in a phase 2b randomized, double-blind clinical trial in adults with chronic HBeAg-positive infection.[30] One hundred and four

individuals were enrolled to receive 1 year of either: telbivudine 400 mg; telbivudine 600 mg; telbivudine 400 mg and lamivudine 100 mg; telbivudine 600 mg and lamivudine 100 mg; or lamivudine 100 mg. At 52 weeks the median changes in HBV DNA concentrations were –6.43, –6.09, –6.40, –6.05, and –4.66 $\log_{10}$ copies/mL, respectively. Ninety patients continued therapy for a further year; all patients who received telbivudine took 600 mg for the second year.[31] After 104 weeks, individuals exposed to telbivudine monotherapy had a 1.3 $\log_{10}$ greater mean viral load reduction compared with those receiving lamivudine monotherapy (–5.2 vs. –3.9 $\log_{10}$ copies/mL, respectively). In the telbivudine monotherapy arm 71% achieved an undetectable viral load compared with 32% in the lamivudine monotherapy arm (P<0.05). Telbivudine monotherapy was associated with greater normalization of serum ALT (81% vs. 47%; P<0.05) and higher rates of HBeAg seroconversion (38% vs. 21%), although the latter was not statistically significant. The rate of treatment failure was significantly lower with telbivudine monotherapy than with lamivudine monotherapy (4.5% vs. 21.1%; P<0.05). There was no significant difference between the use of telbivudine alone and telbivudine/lamivudine in combination.

Phase 3 Trials

The multinational GLOBE study, a phase 3, randomized, double-blind clinical trial compared the use of telbivudine with lamivudine in 1367 treatment-naïve individuals (Table 1).[32-34] Individuals were randomized to receive either lamivudine 100 mg or telbivudine 600 mg for 104 weeks. The primary efficacy endpoint was a therapeutic response, defined as suppression of serum HBV DNA to ≤5 $\log_{10}$ copies/mL along with ALT normalization and/or HBeAg loss. Primary treatment failure was defined by plasma HBV DNA concentrations consistently ≥5 $\log_{10}$ copies/mL. Histological response, reduction in serum HBV DNA, percentage of patients achieving an undetectable HBV DNA by polymerase chain reaction (PCR), HBeAg seroconversion, and safety were also assessed.

In HBeAg-positive individuals at week 52 there was a significant reduction in HBV DNA and a significantly greater clearance of HBV DNA to PCR undetectable in the telbivudine-exposed individuals compared with lamivudine (Table 1). The proportions with ALT normalization, HBeAg loss, and seroconversion were similar in the two groups. More telbivudine-treated patients had an improvement in histology compared with lamivudine-treated patients. Treatment failure was significantly higher in the lamivudine arm compared with the telbivudine arm. In the HBeAg-negative group the proportion achieving a therapeutic response was comparable in the telbivudine and lamivudine groups. HBV DNA fell by more and the proportion of patients achieving undetectable HBV DNA was greater in the telbivudine than the lamivudine group. There was no significant difference in ALT normalization or histological response between the two groups.[32]

Two-year data from the GLOBE study has recently been presented (Table 1).[33,34] Telbivudine treatment continued to be superior to lamivudine in achieving a therapeutic response in HBeAg-positive and HBeAg-negative individuals. In HBeAg-positive patients, the mean reduction in baseline HBV DNA was greater, more patients achieved PCR undetectability, and there was

Table 1. GLOBE trial results at 52 and 104 weeks in HBeAg-positive and HBeAg-negative patients.[32-34]

	Telbivudine	Lamivudine	*P* value
HBeAg-positive, *n*	458	463	
Week 52			
Therapeutic response, %	75.3	67.0	<0.010
Reduction in HBV DNA, $\log_{10}$ copies/mL	6.45	5.54	<0.010
PCR undetectable (<300 copies/mL), %	60.0	40.4	<0.010
ALT normalization, %	77.2	74.9	NS
HBeAg loss, %	25.7	23.3	NS
HBeAg seroconversion, %	22.5	21.5	NS
Improved histology, %	64.7	56.3	<0.010
Treatment failure, %	4.7	13.4	<0.010
Resistance, %	5.0	11.0	<0.010
Week 104			
Therapeutic response, %	63.3	48	<0.050
Reduction in HBV DNA, $\log_{10}$ copies/mL	5.7	4.4	<0.050
PCR undetectable (<300 copies/mL), %	55.6	38.5	<0.050
ALT normalization, %	70	62	<0.050
HBeAg loss, %	35.24	29.2	NS
HBeAg seroconversion, %	29.6	24.7	<NS
Treatment failure, %	4	12	<0.001
Resistance, %	25.1	39.5	<0.001
HBeAg-negative, *n*	222	224	
Week 52			
Therapeutic response, %	75.2	77.2	NS
Reduction in HBV DNA, $\log_{10}$ copies/mL	5.23	4.4	<0.010
PCR undetectable (<300 copies/mL), %	88.3	71.4	<0.010
ALT normalization, %	74.4	79.3	NS
Improved histology, %	66.6	66.0	NS
Treatment failure, %	0.4	2.7	NS
Resistance, %	2.2	10.7	NS
Week 104			
Therapeutic response, %	78	66	<0.050
Reduction in HBV DNA, $\log_{10}$ copies/mL	5.0	4.2	<0.050
PCR undetectable (<300 copies/mL), %	82	56.7	<0.050
ALT normalization, %	78	70	NS
Treatment failure, %	0	3	<0.010
Resistance, %	10.8	25.9	<0.0001

ALT=alanine aminotransferase; HBeAg=hepatitis B e-antigen; HBV=hepatitis B virus; NS=nonsignificant; PCR=polymerase chain reaction.

52-week data reprinted from Lai CL, et al. Telbivudine versus lamivudine in patients with chronic hepatitis B. N Engl J Med. 2007;357:2576-2588, with permission from New England Journal of Medicine.

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less viral resistance in the telbivudine than the lamivudine group. There was no significant difference in HBeAg loss or seroconversion in the overall treatment group, but in a subset of patients with baseline ALT level ≥2 times normal the difference was significant. In HBeAg-negative individuals telbivudine treatment was also associated with a statistically significant reduction in HBV DNA levels, higher rates of nondetectable viremia, and less resistance compared with lamivudine.

In another phase 3 trial comparing telbivudine to lamivudine in Chinese patients, telbivudine was again superior to lamivudine.[35,36] At 52 weeks, among 290 HBeAg-positive patients, mean reductions of serum HBV DNA were significantly greater in telbivudine-treated individuals than those receiving lamivudine (6.3 vs. 5.5 $\log_{10}$; $P<0.001$). Treatment with telbivudine was associated with significantly more HBV DNA undetectability than treatment with lamivudine (67% vs. 38%; $P<0.001$). Telbivudine treatment was also associated with improved ALT normalization (87% vs. 75%; $P=0.007$) and HBeAg loss (31% vs. 20%; $P=0.047$). This study had only a small number of HBeAg-negative individuals ($n=42$), making interpretation of the response in this group more difficult. Overall, however, treatment effects showed similar patterns. Viral resistance was lower in telbivudine-treated individuals compared with lamivudine but this difference was not significant. Both telbivudine and lamivudine were well tolerated with clinical adverse events being similar between the two treatment groups.

A third major study compared the use of telbivudine with adefovir in mainly Asian HBeAg-positive individuals with compensated chronic HBV.[37,38] In this multicenter, open-label study, 135 individuals were randomly assigned to three groups: Group A received telbivudine for 52 weeks, Group B received adefovir for 52 weeks, and Group C received adefovir for 24 weeks followed by telbivudine for the remaining 28 weeks. Results were evaluated at weeks 24 and 52. From 2 weeks of therapy, telbivudine treatment was associated with a consistently lower mean serum HBV DNA level than adefovir therapy. At week 24, a significantly greater HBV DNA reduction from baseline was seen in those individuals exposed to telbivudine compared with adefovir (–6.3 vs. –4.97 $\log_{10}$ copies/mL; $P<0.01$). More patients treated with telbivudine than adefovir had serum HBV DNA levels that were undetectable by PCR (38.6% vs. 12.4%; $P<0.01$). Only 5% of individuals exposed to telbivudine failed to reach a HBV DNA of <5 $\log_{10}$ copies/mL, compared with 42% in the adefovir arm ($P<0.01$). There was no significant difference in HBeAg loss or normalization of ALT levels between the study arms and no difference in adverse events.

In patients switched from adefovir to telbivudine at week 24 (Group C), mean HBV DNA levels rapidly decreased after week 24 such that 8 weeks later levels were nearly identical to those in patients in Group A. At week 52, mean residual HBV DNA levels in Groups A and C differed from those in Group B (3.01 $\log_{10}$ copies/mL and 3.02 $\log_{10}$ copies/mL, respectively, vs. 4.00 $\log_{10}$ copies/mL; $P=0.004$). Reductions in mean serum HBV DNA levels were greater in Groups A and C (–6.56 $\log_{10}$ copies/mL and –6.44 $\log_{10}$ copies/mL, respectively) than in Group B (–5.99 $\log_{10}$ copies/mL). These differences were statistically significant after adjustment for baseline covariates. More patients in Groups A and C than in Group B were PCR-negative at week 52, and more patients in Groups A and C (30% and 26%, respectively) than in Group B

(21%) lost HBeAg, although these differences did not reach statistical significance. There was no significant difference in HBeAg seroconversion or ALT normalization. No patient experienced HBsAg loss or seroconversion.

A small short-term study of 80 HBeAg-positive chronic HBV patients in China compared telbivudine to entecavir.[39] PCR undetectable serum HBV DNA levels at 24 weeks were similar in the telbivudine and entecavir groups (80% vs. 70%, respectively). There were no significant differences in the normalization of ALT levels or in the mean reductions in serum HBV DNA from baseline levels between the two groups at week 12 and 24. More patients in the telbivudine group had HBeAg seroconversion at week 12 than those in the entecavir group (20% vs. 5%; P=0.043); however, there was no significant difference between the two groups at week 24 (27.5% vs. 17.5%). No adverse reactions were found in either group.

Safety

Some nucleoside analogs, particularly those used in treating HIV such as zidovudine and stavudine, have demonstrated clinically limiting delayed toxicities such as peripheral neuropathy, myopathy, and pancreatitis. This cellular toxicity has been attributed to decreased mitochondrial DNA content and altered mitochondrial function, leading to lactic acid production. In vitro, telbivudine had no effect on hepatoma cell line lactic acid production, mitochondrial DNA content, or morphology.[22] In preclinical studies, telbivudine was investigated in rats and monkeys at concentrations substantially higher than the dose used in humans (up to 2000 mg/kg of body weight) and did not identify any safety issues.[40] No significant toxic effects were observed, suggesting a minimal risk of cumulative carcinogenic or reproductive toxicity in humans. In the woodchuck HBV model, telbivudine was well tolerated and caused no drug-related toxicity through 12 weeks of treatment and 4 weeks of follow-up.[22]

In human studies, telbivudine was well tolerated at doses up to 800 mg/day.[28] There were no serious adverse events and no dose-limiting toxicities. All reported adverse events were mild or moderate in intensity and most were not attributed to study treatment. The most common associated side effects included abdominal pain, rash, dizziness, headache, cough, diarrhea, nausea, fatigue, and increased levels of blood creatinine phosphokinase, ALT, and amylase. Malaise, arthralgia, myopathy, and peripheral neuropathy are uncommon.[32,34,38] In the GLOBE study, adverse events occurred with similar frequency in the telbivudine and lamivudine arms, although grade 3 or 4 increases in creatine kinase were more common in patients given telbivudine (12.9% vs. 4.1%; P<0.001).[34] Most creatine kinase elevations were asymptomatic, but the return to baseline values after drug discontinuation took longer in the telbivudine group. No case of lactic acidosis or hepatic steatosis related to telbivudine use has been reported.

Resistance

Antiviral resistance occurs through mutations in the HBV polymerase and is a serious concern with longer-term nucleoside and nucleotide therapy. HBV strains resistant to all of the commonly used agents and, more alarmingly, multidrug-resistant HBV strains have been reported.[41-44] The number of patients with resistant HBV infection

rises with each year of therapy (Table 2). Recent studies suggest that less resistance is observed with newer, more potent agents such as entecavir and tenofovir.[17,18,45] The rapid and profound antiviral effect of telbivudine may thus predict a favorable resistance profile. Conversely, since only a single site substitution in the YMDD motif (M204I) is required to induce telbivudine resistance[46] this agent might have a low genetic barrier to resistance.

In the GLOBE study, virological breakthrough resistance was defined as return of HBV DNA to >5 $\log_{10}$ copies/mL, or increase within 1 $\log_{10}$ copy/mL of the baseline value, or 1 $\log_{10}$ copy/mL increase in viral load above the lowest measured concentration.[34] Per-protocol resistance was lower in the telbivudine group than the lamivudine group for HBeAg-positive (25.1% vs. 39.5%, $P<0.001$) and HBeAg-negative (10.8% vs. 25.9%; $P<0.001$) individuals at 104 weeks (Table 1). Among patients with an undetectable HBV DNA concentration on PCR assay after 24 weeks, rates of telbivudine resistance were <5% suggesting that individuals benefit from rapid suppression of HBV viral load. Following sequencing, all resistance was associated with M204 variants. M204I was the only mutation detected in 16 out of 17 telbivudine patients with resistance; the other patient carried a mixture of M204M/I/V.

In the study comparing telbivudine with adefovir,[38] viral breakthrough (increase in serum HBV DNA >1 log above the nadir value) occurred in four individuals on adefovir and three receiving telbivudine. No breakthroughs occurred in the group who switched from adefovir to telbivudine. All breakthroughs occurred after week 24 in patients with serum HBV DNA levels that remained ≥3 $\log_{10}$ copies/mL at week 24. The signature M204I telbivudine resistance mutation was detected at week 52 in the three telbivudine recipients with breakthrough.

The M204I mutation is the primary basis of telbivudine resistance. This mutation reduces susceptibility to other L-nucleoside analogs (eg, lamivudine and entecavir), but not to the acyclic phosphonates adefovir and tenofovir.[47] In an in-vitro model, adefovir was active against telbivudine-resistant mutants; telbivudine remained active against adefovir mutant strain (N236T), but in the presence of the adefovir-resistant mutant rtA181V, there was a three- to fivefold decrease in telbivudine susceptibility.[48] Thus, there may be benefits to combining telbivudine with these

Table 2. Incidence of hepatitis B virus resistance per year in treatment-naïve patients treated with nucleoside/nucleotide analogs as monotherapy.

Drug	Year 1	Year 2	Year 3	Year 4	Year 5	Reference
Lamivudine, %	24	42	53	70	–	15
Adefovir, %	0	3	11	18	29	16
Entecavir, %	0	<1	<1	<1	–	17
Tenofovir, %	0	–	–	–	–	18
Telbivudine*, %	5	25	–	–	–	32,34

*Results for hepatitis B e-antigen (HBeAg)-positive patients.

agents, in a similar way to the recent studies that have suggested adding adefovir to lamivudine therapy may reduce subsequent adefovir resistance.[49] In an in-vitro system, the combination of telbivudine with adefovir produced greater antiviral effects than adefovir alone with no evidence of cytotoxicity or antiviral antagonism.[50]

Drug Interactions

The risk of emerging resistance to single-agent therapy for chronic HBV infection has increased interest in the role of combination therapy. Studies have evaluated the potential for interaction between telbivudine and other antiviral agents.[51] In healthy adults, subjects received telbivudine 200 mg and lamivudine 100 mg daily, or telbivudine 600 mg and adefovir 10 mg daily, either alone or in combination. Neither drug affected the pharmacokinetic parameters of the other when the drugs were used in combination. The pharmacokinetics of telbivudine at the currently approved dose of 600 mg/day administered in combination with lamivudine has not been assessed, but due to their similar mode of activity and cross-resistance, this is an unlikely combination for clinical use. A clinical trial of telbivudine with lamivudine, however, reported no increased incidence of adverse effects.[30]

Zhou et al. investigated the potential for interaction between telbivudine and tenofovir in 16 healthy volunteers.[52] Pharmacokinetic parameters at steady state were comparable for both medications when administered separately or concurrently. In a separate study, telbivudine pharmacokinetics were unaffected by combined treatment with peginterferon alpha-2a in healthy subjects.[53]

Pharmacoeconomic Considerations

Based on average wholesale prices, telbivudine therapy costs approximately £3500 per patient per year for the management of chronic HBV infection. This is more expensive than lamivudine (~£1000), but similar to adefovir (~£3500), tenofovir (~£3000), or entecavir (~£4000). Wong and Pauker used a Markov cohort simulation to assess the cost-effectiveness of telbivudine compared to lamivudine and found telbivudine use to be favorable in both HBeAg-positive and HBeAg-negative individuals.[54] In a cost-utility analysis, Spackman and Veenstra demonstrated that telbivudine provided treatment benefit (quality-adjusted life year 18.55), but this was less than for entecavir or pegylated interferon.[55] In the UK, the recent National Institute for Health and Clinical Excellence appraisal concluded that telbivudine could not be recommended as a cost-effective use of resources for the treatment of chronic HBV.[56]

CONCLUSIONS

Telbivudine is an L-nucleoside that is highly selective for HBV. Phase 3 studies have concluded that telbivudine is superior to lamivudine in terms of improved therapeutic response and less virological resistance. Telbivudine should not be used in patients harboring lamivudine-resistant mutations because of cross-resistance. Overall, telbivudine appears to be safe and well tolerated, although significant elevations in creatine kinase are observed and a few cases of myopathy have been reported.

Whilst the results of the phase 3 trials were statistically significant, the clinical relevance of the results is questionable. Virological breakthrough in patients with

HBeAg-positive disease was lower with telbivudine therapy than lamivudine, but it was still clinically high. Furthermore, lamivudine is no longer recommended as monotherapy for chronic HBV due to its poor resistance profile and is therefore no longer an appropriate comparator in clinical trials. Recent guidelines recommend starting antiviral therapy in treatment-naïve patients with drugs that have a high genetic barrier to resistance (eg, tenofovir and entecavir) to ensure prolonged viral suppression.[57,58] To date, there are no large studies directly comparing telbivudine with these agents but based on the available evidence, telbivudine is likely to be inferior. Lastly, the cost of antiviral therapy has become increasingly important in the management of chronic HBV due to the frequent need for long-term therapy. In the UK, based on an appraisal of economic models, telbivudine has not been recommended for the treatment of chronic HBV.

In conclusion, telbivudine is a potent inhibitor of HBV replication and is safe and well tolerated. Its use, however, is associated with high incidence of resistance, particularly in patients with high baseline levels of replication and those with detectable HBV DNA after 24 weeks of therapy. As a consequence, American and European guidelines do not recommend telbivudine use unless there are good predictors of response (HBV DNA $<2\times10^6$ IU/mL with HBV DNA PCR negativity at 24 weeks). Instead, drugs with higher genetic barrier to resistance (eg, tenofovir or entecavir) are recommended as first-line agents.

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